Remarks

Claims 104-110 and 112-114 are currently pending and under examination. No claims have been cancelled, amended, or added by this Response. No new matter has been introduced.

Claim Objections

Applicant acknowledges that the Examiner indicated Claim 114 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant believes the arguments presented below obviate the objection to claim 114.

Claim Rejections Under 35 U.S.C. §103

Claims 104-110 and 112-113 stand rejected under 35 U.S.C. § 103(a). The Examiner has maintained the rejection of claims 104-110 and 112-113 as allegedly being unpatentable over McKay et al., U.S. Patent No. 5,877,309 (hereinafter, "McKay"), taken together with Schlom et al., U.S. Patent No. 6,045,802 (hereinafter, "Schlom"). To support his arguments the Examiner cites Arbour et al., *J. Exp. Med.* 195(7):801-810(2002) (hereinafter, "Arbour"), and Sabapathy et al., *J. Exp. Med.* 193(3):317-328(2001) (hereinafter, "Sabapathy").

Applicant respectfully reminds the Examiner that the present application claims benefit of PCT application WO 00/14217 having a filing date of September 3, 1999. The Arbour reference cited by the Examiner has a publication date of February 5, 2001, and the Sabapathy reference has a publication date of April 1, 2002. Thus, these newly cited additional references post-date the filing date for the instant application.

Applicant respectfully submits the Examiner still has not made a *prima facie* case for an obviousness rejection based on a combination of the McKay and Schlom references. In order to make a *prima facie* case for an obviousness rejection based on combining two or more references, the Examiner must show some specific teaching, suggestion, or motivation provided by the references to make the combination. As stated in the previous response, McKay teaches inhibiting cellular proliferation, while Schlom teaches a method for inducing antigen-specific

clonal expansion of T cells, i.e., cellular proliferation, in the immune system. More particularly, McKay teaches inhibiting proliferation of abnormally dividing (viz., cancer) cells by treating them with antisense oligonucleotides targeted to JNK. McKay thus teaches methods for downregulation of JNK. In many cell types of the immune system, including T cells in particular, upregulation of JNK expression plays a pivotal role in inducing an immune response. There is no teaching, suggestion, or motivation provided in McKay and/or Schlom to combine a method for downregulating JNK (as in McKay) with a method in which JNK may be upregulated (as in Schlom) as these methods appear to be mutually contradictory.

To bolster his previous arguments the Examiner has cited Sabapathy as providing support for his argument that McKay and Schlom may be combined to render the claimed invention obvious. The Examiner cites Sabapathy as teaching that JNK1 is necessary for efficient T cell proliferation and IL-2 production and that JNK2 has no effect on mature T cell proliferation. Applicant respectfully asserts that Sabapathy teaches a role for JNK2 in mature T cell proliferation. The abstract of Sabapathy states that "[a]lthough T cells express both JNK1 and JNK2 isozymes, the absence of JNK2 alone can result in...defective mature T cell proliferation" and "JNK 1 and JNK2 control similar functions during T cell maturation through differential targeting of distinct substrates." As shown in Figure 5 on page 323 of Sabapathy, "defective mature T cell proliferation" refers to impaired, i.e., reduced, T cell proliferation. The abstract of Sabapathy goes on to state that "Importantly, T cell function was compromised in *Jnk1*+/- *Jnk2*+/- double heterozygous mice, indicating that JNK1 and JNK2 play similar roles in regulating T cell function." It would appear then that the combined teachings of McKay and Sabapathy suggest that antisense-mediated downregulation of JNK1 and/or JNK2 would be expected to inhibit T cell proliferation and function. Such inhibition of T cell proliferation and function is directly opposite of what would be desired when administering a tumor antigen in order to treat a tumor. Applicant thus respectfully submits that Sabapathy serves only to bolster Applicant's position that McKay cannot and would not be combined with Schlom, rather than the Examiner's position with respect to McKay and Schlom.

For the avoidance of any doubt, Sabapathy alone combined with Schlom also cannot render the claimed invention obvious, at least for the reason that neither Sabapathy nor Schlom

teaches treatment of a subject having a tumor by administering any oligonucleotide. In addition, it would not be proper to combine Sabapathy and Schlom, as Sabapathy is not available as a prior art reference.

The Examiner cites Arbour as teaching that mice lacking JNK2 show expansion of T cells. It should be noted here that Arbour provides a direct teaching away not only from Sabapathy but also from McKay. Arbour teaches that "JNK2 plays a role in control of CD8+ T cell expansion in vivo" (abstract). In contrast to Sabapathy, Arbour also teaches that "JNK1 and JNK2 assume distinctly different functions in CD8+ T cell activation and expansion" (page 802, column 1). The data shown in Figure 1 of Arbour shows that "JNK2 -/- mice showed a statistically significant increase in the relative expansion of virus specific CD8+ T cells when compared with JNK+/+" (page 803, column 2).

These data are directly contradictory to the teachings of both McKay and Sabapathy. MacKay teaches the use of antisense oligonucleotides to JNK to decrease cell proliferation. Sabapathy teaches that absence of JNK2 results in decreased T-cell proliferation. In contrast, Arbour teaches that absence of JNK2 results in increased CD8+ T-cell proliferation in response to viral infection. Arbour therefore amounts to a direct teaching away from McKay, and it is inconsistent with Sabapathy. Therefore, Arbour, either with or without Sabapathy, does not provide support or motivation to combine McKay and Schlom.

For the avoidance of any doubt, Arbour alone combined with Schlom also cannot render the claimed invention obvious, at least for the reason that neither Arbour nor Schlom teaches treatment of a subject having a tumor by administering any oligonucleotide. In addition, it would not be proper to combine Arbour and Schlom, as Arbour is not available as a prior art reference.

Applicant maintains that, as McKay and Schlom are mutually incompatible, there is no teaching, motivation, or suggestion to combine the teachings of McKay and Schlom as proposed by the Examiner. Applicant therefore respectfully reiterates that the Examiner has not made a *prima facie* case for making the obviousness rejection.

In view of the foregoing, Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 104-110 and 112-113 under 35 U.S.C. 103.

Without making a formal enablement rejection, the Examiner goes on to assert at the bottom of page 5 of the Office Action that if Applicant were correct [about the combination of McKay and Schlom], "the claimed method would not be considered enabled for the full scope of the method because the method taught by McKay and Schlom is embraced by the claimed invention and the instant specification does not teach the skilled artisan that using the method taught by McKay and Schlom would be inoperable and the claimed method is unpredictable". Applicant respectfully submits that this hypothetical rejection would appear to be based on the invalid assumption that there is a method taught by McKay and Schlom. As stated above, the combination of McKay and Schlom is not proper and they do not together comprise a "method". Applicant therefore respectfully submits that the Examiner has not properly made even a hypothetical enablement rejection.

On page 6 of the Office Action the Examiner asserted that Applicant's arguments concerning the 103 rejection in the previous Response to Office Action, that there would be no reasonable expectation of success in arriving at the instantly claimed invention by combining the methods of McKay and Schlom as they appear to be mutually contradictory, are not persuasive since "there is no evidence of record to support applicant's assertion." The Examiner cites MPEP 2145, which states that Applicant's argument does not replace factual evidence *where evidence is necessary*. Applicant respectfully submits that it is normally not necessary for an applicant to provide factual evidence in order to establish that a combination of references proposed by an examiner is improper. In this instance Applicant has made reasoned arguments based on analysis of what the references cited by the Examiner actually teach, rather than merely making an assertion about "what seems to follow from common experience" (MPEP 2145).

Applicant submits that the reasons already of record, and as further supported in this Response, amply demonstrate that even if a skilled person were to combine McKay and Schlom as suggested by the Examiner, there would be no reasonable expectation of arriving at the claimed invention. More specifically, because the teachings of McKay relate to downregulation of JNK to decrease cell proliferation and the teachings of Schlom relate to upregulation of an

immune response with enhanced T cell proliferation, the skilled person would have no reasonable expectation that combining McKay with Schlom would result in the claimed invention. For reasons set forth above, the mutually contradictory teachings of Sabapathy and Arbour, neither of which is prior art, can serve only to underscore this absence of reasonable expectation of arriving at the claimed invention through combining McKay with Schlom.

Applicant argued in the previous Response that administration of an antisense oligonucleotide specific for JNK (as in McKay) to cells which are to be activated to produce an immune response against a tumor-specific antigen (as in Schlom) would be expected to have the effect of inhibiting the normal JNK activities involved in and necessary for mounting an effective immune response. As discussed above, the teachings of McKay and Sabapathy support the idea that inhibition of JNK results in impaired T cell activation. The teachings of Schlom support the idea that an immune response against a tumor-specific antigen includes T cell proliferation. These teachings alone are enough to support the Applicant's assertion that the combination of McKay and Schlom would not reasonably be expected to result in the claimed invention.

For the record, Applicant respectfully submits that the finality of the Office Action mailed on July 7, 2005, is improper to the extent that the citation of Sabapathy and Arbour by the Examiner represents new grounds for the rejection under 35 U.S.C. 103.

Summary

No claims are canceled, amended, or added by this Response. Arguments are set forth to overcome all claim rejections and objection to claim 114. A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee

occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Wagner et al., Applicant

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